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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,321	07/13/2001	Yousuke Takahama	31671-173265	2334

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,321	TAKAHAMA, YOUSUKE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the restriction requirement received on 11/03/03 has been entered. Applicant's election without traverse of the subject matter of Group I, claim 1-12, is acknowledged. Claims 1-19 are pending in the instant application. Of these, claims 13-19 are hereby withdrawn from prosecution as being drawn to subject matter non-elected without traverse in the response received on 11/03/03. Claims 1-12 are currently under examination. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 recites a method "characterized" in that the foreign DNA is transferred into thymus mediated by fetal T lymphocytes. The use of the word "characterized" renders the claim vague and indefinite in that the claim does not clearly set forth any particular method steps. While the method is "characterized" by foreign DNA transfer, it is not clear that the method

actually comprises the direct administration of foreign DNA or of foreign DNA transferred fetal T lymphocytes. From the claim language, it is possible that foreign DNA or foreign DNA transferred fetal T lymphocytes are already present in mammal and that the method somehow occurs by the DNA or T lymphocytes traveling to the thymus. It is suggested that the applicant amend the claims to recite particular method steps, i.e. " a method .... comprising the administration of foreign DNA or foreign DNA transferred fetal T lymphocytes directly into the thymus...".

In addition, in claims 1, 3-8, and 10-12, the claims recite that the foreign DNA is transferred into thymus "mediated" by fetal T lymphocytes. It is unclear what the applicant intends to encompass by the term "mediated". As written, the claims read on the free foreign DNA, not present in a cell, and on foreign DNA present in a cell. It is unclear as to whether the fetal T lymphocytes contain the foreign DNA or whether the lymphocytes simply facilitate the transfer of free foreign DNA or DNA present in another type of cell into the thymus.

Further in regards to claims 8 and 9, the claims are confusing in that it is unclear what is meant by a "foreign DNA in gene therapy" or a "foreign-DNA-transferred fetal T lymphocyte in gene therapy". If the applicant intends that the foreign-DNA encodes a therapeutic gene useful for gene therapy, then it is suggested that the claims reflect this limitation. In addition, claim 9 states that immune response is avoided by introducing a foreign-DNA transferred fetal T lymphocyte into thymus, "and by expressing a foreign DNA in thymus organ". The wording of this claim makes it unclear whether the foreign DNA expressed is in fact expressed from the transferred fetal T lymphocytes or whether the foreign DNA is separate from the foreign DNA present in these cells. Clarification is requested.

Information Disclosure Statements

The information disclosure statement filed 7/13/01 fails to fully comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citations listed as citation numbers AG-AI, AK, and AM fail to include the title of journal in which these articles are published. The references have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any resubmission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all requirements for statements under 37 CFR 1.97(e). See MPEP § 609 subsection III, C(1).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335. The applicant claims methods of acquiring immunological tolerance to a foreign DNA or methods of sustaining a gene therapeutic

effect characterized by the transfer of foreign DNA into thymus mediated by fetal T lymphocytes. The applicant further claims said methods wherein the foreign DNA comprises an adenoviral vector, or wherein the foreign DNA comprises a gene which causes allergy or autoimmunity, or which is a peptide therapeutic medicament. As noted in the above rejection of the claims under 35 U.S.C. 112, second paragraph, the claims as written lack a specific method step and are indefiniteness in their recitation of "characterized by" and "mediated". In the spirit of compact prosecution, the claims have been construed to read on the administration of foreign DNA to fetal thymus for the purposes of prior art analysis.

DeMatteo et al. teaches the direct injection of a recombinant adenovirus encoding a gene of interest into fetal thymus resulting in the induction of tolerance to the adenoviral proteins and encoded foreign gene product (DeMatteo et al., page 5330, abstract). Specifically, DeMatteo et al. demonstrated a substantial increase in sustained gene expression following intravenous or intratracheal administration of recombinant adenovirus if the host had first received an intrathymic injection of the recombinant adenovirus (DeMatteo et al., Figure 1). In fact, DeMatteo et al. teaches detection of transgene expression from adenovirus infected cells up to 260 days as compared to less than 14 days in untreated hosts (DeMatteo et al., Figure 1). In addition, DeMatteo et al. teaches that the adenovirus can encode therapeutic proteins such as the cystic fibrosis membrane conductance regulator gene or proteins associated with states of autoimmunity or allograft rejection (DeMatteo et al., page 5334, column 2, last paragraph). Thus, by teaching all the elements of the claims as written, DeMatteo et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462. The applicant claims methods of acquiring immunological tolerance to a foreign DNA or methods of sustaining a gene therapeutic effect characterized by the transfer of foreign DNA into thymus mediated by fetal T lymphocytes, and in particular by the introduction of foreign DNA transferred fetal T lymphocytes into the thymus. The applicant further claims said methods wherein the foreign DNA comprises an adenoviral vector, or wherein the foreign DNA

comprises a gene which causes allergy or autoimmunity, or which is a peptide therapeutic medicament.

Ilan et al. teaches central tolerance induction in adult mammals by directly injecting either recombinant adenovirus encoding a therapeutic gene or cells transduced with recombinant adenovirus into the thymus (Ilan et al., page 2640, abstract). In particular, Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640). Ilan et al. further teaches that protein other than BUGT1 can be used to generate central tolerance, such as proteins associated with autoimmune disease or allograft rejection (Ilan et al., page 2641, column 1).

Ilan et al. differs from the instant claims in that Ilan et al. teaches the use of adenovirus infected hepatocytes rather than adenovirus infected fetal T lymphocytes. DeMatteo et al. supplements Ilan et al. by teaching that adenovirus is capable of infecting fetal T lymphocytes in fetal thymus *in vivo* resulting in tolerance induction (DeMatteo et al., page 5330, abstract, and Figure 1). Bakker et al. further supplements Ilan et al. and DeMatteo et al. by teaching methods of infecting fetal T lymphocytes with recombinant adenovirus *in vitro* in fetal thymic organ culture (Bakker et al., page 3457). Bakker et al. further teaches that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456).

Motivation to substitute fetal T lymphocytes for hepatocytes in the methods of Ilan et al. is provided by both Ilan et al. and DeMatteo et al. In the methods of central tolerance taught by

Ilan et al., suppression of mature T cells by antilymphocyte serum was used to prevent reactivity of mature T cells with the adenoviral proteins (Ilan et al., page 2640). DeMatteo et al. also teaches that in adult mice, as opposed to neonatal mice, induction of tolerance by intrathymic administration of adenovirus requires suppression of mature T cells and is further aided by using a cellular carrier to prevent viral extravasation into the periphery (DeMatteo et al., page 5334, column 2). In view of the need to suppress mature T cells in order to effectively achieve central tolerance by administering adenoviral infected cells to the thymus, the skilled artisan would have been motivated to re-introduce fetal T lymphocytes into the thymus in order to stimulate repopulation of the periphery with mature T lymphocytes. Thus, based on the motivation to introduce fetal T lymphocytes to repopulate mature T lymphocytes in hosts treated with antilymphocyte serum, it would have been *prima facie* obvious to the skilled artisan to substitute fetal T lymphocytes for the hepatocytes in the methods of inducing central tolerance to recombinant adenoviruses taught by Ilan et al. Further, based on the successful infection of fetal T lymphocytes taught by Bakker et al., the skilled artisan would have had a reasonable expectation of success in infecting fetal T lymphocytes with the recombinant therapeutic adenoviruses taught by Ilan et al. and using those infected fetal T lymphocytes to induce central tolerance in adult hosts following intrathymic injection.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER